



Recent progress in host immunity to avian coccidiosis: IL-17 family cytokines as sentinels of the intestinal mucosa



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ABSTRACT

The molecular and cellular mechanisms leading to immune protection against coccidiosis are complex and include multiple aspects of innate and adaptive immunities. Innate immunity is mediated by various subpopulations of immune cells that recognize pathogen associated molecular patterns (PAMPs) through their pattern recognition receptors (PRRs) leading to the secretion of soluble factors with diverse functions. Adaptive immunity, which is important in conferring protection against subsequent reinfections, involves subtypes of T and B lymphocytes that mediate antigen-specific immune responses. Recently, global gene expression microarray analysis has been used in an attempt to dissect this complex network of immune cells and molecules during avian coccidiosis. These new studies emphasized the uniqueness of the innate immune response to *Eimeria* infection, and directly led to the discovery of previously uncharacterized host genes and proteins whose expression levels were modulated following parasite infection. Among these is the IL-17 family of cytokines. This review highlights recent progress in IL-17 research in the context of host immunity to avian coccidiosis.

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1. Introduction

Coccidiosis is one of the most economically important diseases of chickens (Allen and Fetterer, 2002; Williams, 2002; Shirley and Lillehoj, 2012). The etiologic agent of avian coccidiosis is *Eimeria*, an apicomplexan protozoan parasite encompassing over 1,700 species that infect avian, piscine, reptilian, and mammalian (non-human) hosts. Seven species of *Eimeria* colonize the intestinal tract of domestic chickens, *Eimeria acervulina*, *Eimeria tenella*, *Eimeria maxima*, *Eimeria necatrix*, *Eimeria brunetti*, *Eimeria mitis* and *Eimeria praecox*. Infectious parasites invade intestinal epithelial cells, eliciting a variety of clinical manifestations including necrotic gut lesions, inefficient feed utilization, impaired growth rate, and, in severe cases, mortality. The parasite's life cycle includes intracellular and extracellular as well as asexual and sexual stages (Hammond, 1982). Each stage is characterized by distinctive parasite life forms, including the trophozoite, schizont, merozoite, microgamete, macrogamete, sporozoite, and oocyst. Currently, the poultry industry relies heavily on prophylactic in-feed anticoccidial drugs to suppress the infectious cycle and prevent coccidiosis outbreaks

(Chapman, 2009). While prophylactic medication has been relatively successful in controlling avian coccidiosis in commercial production facilities, alternative strategies are needed due to the emergence of drug-resistant parasites and increasing government regulations on the use of anticoccidial drugs (Lillehoj and Lee, 2012). Further understanding of the complex interplay between the chicken host and coccidian parasites will be crucial for the design and implementation of any new approaches against this disease.

Eimeria parasites are highly immunogenic in chickens, and primary infections can stimulate protective immunity to subsequent challenge by the homologous parasite (Lillehoj and Lillehoj, 2000; Allen and Fetterer, 2002). However, heterologous cross-species protection is weak. Over the past four decades, the nature of host protective immunity to coccidiosis has been the subject of many studies (Shirley and Lillehoj, 2012). Early investigations in mice by Rose and colleagues (Rose and Hesketh, 1979, 1982; Rose et al., 1979; Wakelin et al., 1993) showed T lymphocytes and their cytokines were essential for immunity against *Eimeria* infection in both mammalian and avian species. The role of B cells depended on the nature of the infection. Oocyst production in bursectomized (B cell deficient) chickens following primary infection with *E. maxima* or with *E. acervulina* was increased and the clinical effects of infection with *E. maxima* were greater compared with non-bursectomized controls. Following secondary reinfection, however, the B cell deficient chickens retained immunity. Further, it became clear

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that in coccidia-immune hosts, parasites entered the gut early after infection, but were prevented from further development. This natural arrest in the parasite life cycle suggested that chickens acquired protective immunity following primary coccidia infection. In support of this hypothesis, peripheral blood lymphocytes (PBLs) and splenocytes from *E. maxima*-immune chickens protected syngeneic recipients against live parasite challenge following adoptive transfer of the immune cells (Rose and Hesketh, 1982). Subsequently, protective immunity against *E. tenella* reinfection was shown to be abrogated in chickens treated with the T cell immunosuppressant, cyclosporin A, compared with untreated controls, again emphasizing the importance of cellular immune mechanisms (Lillehoj, 1987).

Cytotoxic T lymphocytes expressing the CD8 cell surface antigen were shown to be markedly increased in chickens soon after a primary infection, further suggesting the activation of an adaptive cellular immune response (Lillehoj and Bacon, 1991; Breed et al., 1996, 1997). Increased cytotoxic T cells were accompanied by greater production of the proinflammatory cytokine, interferon- γ (IFN- γ) (Choi et al., 1999b), which was shown to inhibit parasite development intracellularly (Lillehoj and Choi, 1998). With the recent availability of chicken lymphocyte-specific immune reagents and methodologies, the nature of the T lymphocytes involved in host protective immunity have become more evident (Lillehoj, 1991, 1998; Lillehoj et al., 1988). For example, flow cytometric analyses of intestinal intraepithelial lymphocytes (IELs), immune cells present within the epithelial layer of intestinal linings, led to the identification of an innate immune response in naïve chickens and an adaptive response in previously infected chickens (Lillehoj, 1994). Additional studies led to the characterization of IEL subtypes responsible for local defense against *Eimeria* in the gut (Hong et al., 2006b,d).

Extensive experimental evidence now supports the notion that the manner through which chicken lymphocytes mediate antigen-specific protective immunity in avian coccidiosis involves their secreted products (Lillehoj and Lillehoj, 2000; Lillehoj et al., 2004, 2012; Yun et al., 2000). Among the major chicken cytokines and chemokines, and their cell surface receptors, that have been described in this response are IFN- γ , interleukin-1 (IL-1), IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-15, IL-16, IL-17, IL-18, tumor necrosis factor- α (TNF- α), lipopolysaccharide-induced TNF- α factor (LITAF), TNF- α superfamily 15 (TNFSF15), transforming growth factor- β 1 (TGF- β 1), TGF- β 2, TGF- β 3, TGF- β 4, and granulocyte-macrophage colony-stimulatory factor (GM-CSF) (Avery et al., 2004; Choi et al., 1999a; Degen et al., 2004; Hong et al., 2006c; Jakowlew et al., 1991; Jeong et al., 2011, 2012; Koskela et al., 2004; Lillehoj et al., 2004; Min and Lillehoj, 2002, 2004; Min et al., 2002; Pan and Halper, 2003; Rothwell et al., 2004; Schneider et al., 2000, 2001; Song et al., 1997; Staeheli et al., 2001; Yoo et al., 2009; Zhang et al., 1995).

The IL-17 family of cytokines is among the most recently described mediators of immunity in avian coccidiosis (Min and Lillehoj, 2002; Hong et al., 2008; Kim et al., 2012). In mammals and avians, IL-17 cytokines are produced by T helper 17 (Th17) CD4 $^{+}$ T cells, a subpopulation of cells phenotypically and functionally distinct from the classical Th1 and Th2 lymphocyte lineages (Iwakura et al., 2011). Six IL-17-related cytokines have been described in mammals (IL-17A, -17B, -17C, -17D, -17E, and -17F) with varying degrees of intermolecular amino acid sequence homology and biological function. IL-17A (the original IL-17) is the prototypical cytokine produced by Th17 cells and plays a key role in mediating inflammation early during the course of an infection and prior to the onset of adaptive T cell responses. The indispensable role for IL-17A in host defense against infectious pathogens is supported by various *in vivo* mammalian infection model systems (Iwakura et al., 2011). IL-17A, in concert with IL-17F, drives the early phases

of an immune response by increasing the expression of genes encoding other proinflammatory cytokines, chemokines, antimicrobial peptides, and matrix metalloproteinases by lymphocytes, fibroblasts, endothelial cells, and epithelial cells (Kinugasa et al., 2000; Iwakura et al., 2011). Additionally, both cytokines synergize with tumor necrosis factor- α (TNF- α) and IL-1 β to amplify and sustain these proinflammatory responses. Finally, IL-17A is instrumental in intestinal homeostasis and plays an important role in maintaining the integrity of mucosal barriers (Kinugasa et al., 2000).

2. Immune responses to avian coccidiosis

2.1. Innate immune responses to avian coccidiosis

Innate and adaptive immunities mediate the host response against avian coccidiosis (Dalloul and Lillehoj, 2006; Lillehoj et al., 2012). Innate immunity represents the first line of defense against invading pathogens. Innate immune responses are activated when conserved components of pathogens, the pathogen associated molecular patterns (PAMPs), engage specific cell surface receptors, or pattern recognition receptors (PRRs). PAMPs constitute a broad group of chemically diverse molecules (proteins, lipids, carbohydrates, and nucleic acids) derived from bacteria, viruses, fungi, and protozoa (Kumar et al., 2011; Gazzinelli and Denkers, 2006). The Toll-like receptors (TLRs) were the first PRRs described in mammals (Medzhitov, 2001; Lemaitre, 2004), and TLR homologues have been identified in chickens (Brownlie and Allan, 2011; Temperley et al., 2008; Summers et al., 2011). PRRs, in general, and TLRs, in particular, are expressed by a variety of cell types, including dendritic cells, monocytes, macrophages, and epithelial cells. The involvement of intestinal dendritic cells in the initiation of innate immune responses to avian coccidiosis has been documented (Del Cacho et al., 2011, 2012). The TLR ligand, profilin, is a 19 kDa protein that is highly conserved among all Apicomplexa protozoa, including *Eimeria*, and is expressed during most stages of the parasite's life cycle (Fetterer et al., 2004). The profilin of *Toxoplasma gondii*, toxofilin, plays a critical role in CD4 $^{+}$ T cell-driven immunity against the pathogen (Yarovinsky et al., 2005, 2006). Toxofilin binds to TLR11, inducing a potent IL-12 response in murine dendritic cells. *Eimeria* profilin induced antigen-specific proliferation and IFN- γ production by chicken splenic lymphocytes (Lillehoj et al., 2000), although it's cognate TLR receptor in avians has not been identified.

Natural killer (NK) cells constitute another subclass of lymphocytes that mediate innate immunity during avian coccidiosis (Lillehoj, 1989). High-throughput nucleotide sequence analysis of an intestinal cDNA library from *Eimeria*-infected chickens led to the identification of a novel peptide with antiparasitic activity secreted by NK cells (Hong et al., 2006a). This antimicrobial peptide possessed an amino acid sequence that was homologous to mammalian NK lysin. NK lysin transcript levels were increased in CD4 $^{+}$ and CD8 $^{+}$ intestinal IELs following *E. maxima* infection. Another player of innate immunity is the macrophage, which is involved in different phases of the host immune response to coccidia (Lillehoj et al., 2004). Of relevance to avian coccidiosis, macrophage migration inhibitory factor (MIF) plays an important role in host defense against a variety of microorganisms, including protozoan parasites (Sun et al., 1996). MIF is highly conserved in invertebrates and vertebrates, and is produced by monocytes, macrophages, T cells, and non-lymphoid cells (Calandra et al., 1994). Mammalian MIF induces the expression of proinflammatory mediators, including IL-1 β , IL-6, IL-8, IFN- γ , and TNF- α (Vermeire et al., 2008). *E. tenella* infection induced high levels of the chicken MIF gene transcript in the gut (Jang et al., 2011). *In vitro* treatment of

chicken macrophages with chicken MIF recombinant protein increased the levels of transcripts encoding IL-6, IL-17, and TNFSF15, but a decreased the level of IL-8.

2.2. Adaptive immune responses to avian coccidiosis

The adaptive immune system is composed of highly specialized immune cells that prevent pathogen colonization of and growth within the host. In both mammals and avians, adaptive immunity is regulated by antigen-specific receptors on B cells (surface immunoglobulins) and T cells (T cell receptors, or TCRs), the latter of which can be further subdivided into $\alpha\beta$ TCR and $\gamma\delta$ TCR heterodimeric receptors. Three different antibody isotypes are recognized in birds: IgM, IgA, and IgY (the equivalent of mammalian IgG). The role of parasite specific antibodies in serum and mucosal secretions has been studied in avian coccidiosis (Girard et al., 1997). Maternal IgY is concentrated in the yolk sac of the egg where it is transported to the embryo late during embryogenesis. Thus, maternal IgY is considered to mediate passive immunity (Wallach, 2010; West et al., 2004). While the B cell depletion studies mentioned above (Lillehoj, 1987) suggested that antibodies do not play an appreciable role in protective immunity against avian coccidiosis, other studies have clearly indicated a role for passive humoral immunity to *Eimeria* infection. Young birds receiving passively transferred antibodies from breeding hens hyperimmunized with *E. maxima* antigens were protected against challenge infection by viable parasites (Wallach et al., 1992). Passive immunization of newly hatched chickens with egg yolk IgY antibodies obtained from hens immunized with *E. tenella*, *E. acervulina* and *E. maxima*, provided protection against live challenge infection by the homologous parasite (Lee et al., 2009a,b).

Cell-mediated immunity (CMI) includes antigen-specific and non-specific activation of T lymphocytes, NK cells, and macrophages. The major T cell subsets are CD4⁺ T helper (Th) cells and CD8⁺ cytotoxic T lymphocytes (CTLs), both of which are involved in the host response to *Eimeria* infection (Lillehoj, 1998; Lillehoj and Lillehoj, 2000; Trout and Lillehoj, 1996; Yun et al., 2000). The presence of *Eimeria*-specific T cells was initially demonstrated by antigen-specific proliferation of T lymphocytes in a recall assay using parasite-immune chickens (Lillehoj, 1986; Vervelde et al., 1996). Following primary and secondary infections with *E. acervulina*, an increased percentage of intestinal T cells bearing $\gamma\delta$ TCRs was observed in the intestinal duodenum, concurrent with increased levels of IL-2 gene transcripts in these cells (Choi and Lillehoj, 2000). Increased numbers of CD8⁺ T cells were noted in intestinal IELs following infection with *E. acervulina* (Vervelde et al., 1996). In *E. tenella*-infected chickens, the number of CD4⁺ lymphocytes in the ceca increased significantly two days after infection, while CD4⁺ and CD8⁺ T cells infiltrated the lamina propria (Vervelde et al., 1996). CD3⁺, CD8⁺, and $\alpha\beta$ TCR⁺ T cells in *Eimeria*-immune chickens were localized in the gut within the vicinity of parasite sporozoites (Lillehoj and Trout, 1994). Although the detailed mechanisms mediated by various T lymphocyte subpopulations in host protection against avian coccidiosis remain to be determined, these results suggest that T cells are important for protection against avian coccidiosis.

3. Th1, Th2, and Th17 cytokines as mediators of immunity to avian coccidiosis

During T cell development, at least three distinct subsets of T helper cells have been delineated: Th1, Th2, and Th17 (Szabo et al., 2003; Korn et al., 2009; Hundorf et al., 2012; Pappu

et al., 2010, 2012). All three subsets of cells are involved in protective immunity against infectious agents, and the Th1/Th2 balance, in particular, is critical for protection against intracellular pathogens, including *Eimeria* (Cornelissen et al., 2009; Haritova and Stanilova, 2012). In general, Th1 cells regulate immunity to intracellular pathogens, Th2 cells control immune responses against extracellular microorganisms, and Th17 cells are involved in more general aspects of inflammation and some components of the response to extracellular microbes. The cytokine environment in the immediate vicinity of the differentiating T helper cells regulates which cells are produced. IFN- γ drives Th1 cell production, while IL-4 and IL-10 inhibit Th1 cell production. Conversely, IL-4 drives Th2 cell production and IFN- γ inhibits Th2 cells. It is less clear which cytokines contribute to Th17 formation, but TGF- β , IL-6, IL-21, and IL-23 have been implicated. The major cytokines produced by Th1 cells are IFN- γ , IL-10, and TGF- β , those produced by Th2 cells are IL-4, IL-5, and IL-13, and those of Th17 cells are IL-17A/F, IL-21 and IL-22.

Avian cytokines have been implicated in initiating, sustaining, and regulating protective immunity against avian coccidiosis (Lillehoj et al., 2004; Lowenthal et al., 1999; Yun et al., 2000). Compared with their mammalian counterparts, however, relatively slow progress has been made in characterizing these molecules. The chicken IFN- γ gene has been cloned and shown to inhibit the intracellular development of *E. tenella* following *in vitro* infection (Lillehoj and Choi, 1998; Lillehoj et al., 2004). After *E. acervulina* infection, IFN- γ mRNA expression was detected in the cecal tonsils and spleen of SC chickens, a genetic line that is comparatively resistant to experimental avian coccidiosis (Choi et al., 1999b). These results provided a rational basis for the use of IFN- γ as a vaccine adjuvant against *Eimeria* infection (Lillehoj et al., 2005b). IL-1 β expression was detected in the intestine after infection with *E. tenella* or *E. maxima* (Laurent et al., 2001). After primary and secondary infections with *E. acervulina*, increased levels of IL-2 transcripts were observed in the spleen and intestine (Choi and Lillehoj, 2000; Lillehoj et al., 2001). IL-6 transcripts were detected during the first few hours post-infection and were suggested to be involved in the development of acquired immunity to avian coccidiosis (Lynch et al., 2000). Finally, TNF-like factors have been described in chickens (Hong et al., 2006c; Park et al., 2007) and have been detected in avian peripheral blood-derived macrophages stimulated by sporozoites and merozoites of *E. tenella* (Zhang et al., 1995). *In vivo* treatment of chickens with polyclonal TNF antibodies partially abrogated *E. tenella*-induced body weight loss.

More recently, functional genomics and bioinformatics technologies have been applied to investigate the host-pathogen interactions during avian coccidiosis, and particularly to elucidate the role of cytokines in regulating these interactions (Hong et al., 2006b; Kim et al., 2009, 2010, 2011; Lillehoj et al., 2008; Min et al., 2004). The application of high-throughput nucleotide sequencing of expressed sequence tag (EST) cDNA libraries from intestinal IELs of *Eimeria*-infected chickens led to the identification of additional cytokines, not mentioned above, that are involved in the host response to avian coccidiosis (Min et al., 2005). Among these were chicken IL-16 (Min and Lillehoj, 2004) and IL-17 (Min and Lillehoj, 2002). New candidate genes that influence host immune responses to *Eimeria* also have been identified using global gene expression analysis of chicken macrophage and intestinal IEL cDNA microarrays (Kim et al., 2009, 2010, 2011; Min et al., 2003). Finally, recent studies with quantitative real-time PCR techniques have identified more than 30 different cytokines and chemokines involved in coccidia infection, further illustrating the complexity of the host immune response to *Eimeria* parasites (Hong et al., 2006a,b).

4. The IL-17 family of cytokines

4.1. Mammalian IL-17s

The IL-17 family consists of IL-17A (also called IL-17 or CTLA-8), IL-17B, IL-17C, IL-17D, IL-17E (also called IL-25), and IL-17F. All IL-17 genes that have been examined in humans and various animal species, with few exceptions, are composed of three exons separated by two introns (Korenaga et al., 2010; Lubberts, 2008; Moseley et al., 2003; Reynolds et al., 2012). At the protein level, while these 20–30 kDa molecules share limited amino acid sequence identities amongst themselves (20–50%), all retain four conserved cysteine residues that form two intrachain disulfide bonds. Molecular modeling studies revealed that IL-17 proteins may adopt a “cysteine knot” fold commonly seen in nerve growth factor and other neurotrophins (Zhang et al., 2011). The IL-17 receptor (IL-17R) family includes five molecules, IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE. These single-pass transmembrane receptors possess several conserved structural characteristics, including an extracellular fibronectin III-like domain and a cytoplasmic SEF (similar expression to FGF)/IL-17R (SEFIR) domain (Gaffen, 2009; Iwakura et al., 2011; Moseley et al., 2003). IL-17R genes are clustered together on their respective human and mouse chromosomes, and their genomic structure is relatively more complex than that of IL-17 genes, being composed of between 11 and 19 exons. Mechanistically, IL-17 homo- or heterodimers act through engagement of heterodimeric IL-17Rs (Iwakura et al., 2011; Lee et al., 2001). For example, the IL-17A/IL-17A and IL-17F/IL-17F homodimers, as well as the IL-17A/IL-17F heterodimer, bind to an IL-17RA/IL-17RC heterodimer.

IL-17A and IL-17F are the best characterized members of the IL-17 family. These two genes are syntenic in mammals and avians. However, the arrangement of the mammalian IL-17A and IL-17F genetic loci, and their adjacent genes, are inverted compared with the corresponding avian genes (Fig. 1) (Hymowitz et al., 2001; Iwakura et al., 2011; Kawaguchi et al., 2001; Kim et al., 2012). This gene arrangement suggests the occurrence of a chromosomal inversion subsequent to the existence of the most recent common ancestor of mammals and birds about 300 million years ago (Kumar and Hedges, 1998). Human IL-17A was originally termed cytotoxic T lymphocyte-associated antigen-8 (CTLA-8) (Rouvier et al.,

1993). Mammalian homologues have been identified in mouse, pig, cow, dog, and horse (Debrue et al., 2005; Katoh et al., 2004; Macoux et al., 2007; Riollet et al., 2006; Yoo et al., 2009; Yao et al., 1995). The IL-17A gene was first identified from a murine T cell hybridoma that showed sequence homology to the open reading frame 13 of *Herpesvirus saimiri* (HVS13) (Moseley et al., 2003; Rouvier et al., 1993). Human IL-17A is a protein of a 155 amino acids with a monomer molecular weight of 20 kDa. Its disulfide-linked dimer is secreted as a 30–38 kDa glycoprotein (Kono et al., 2011; Yao et al., 1995). IL-17F (or ML-1), a protein of 163 amino acids, was initially discovered through the analysis of genes homologous to IL-17A (Hymowitz et al., 2001; Kawaguchi et al., 2001, 2003). These two molecules share the greatest amino acid sequence identity (approximately 50%) among all IL-17 family members.

The biological activities of IL-17A and IL-17F include stimulation of the production of antimicrobial peptides, such as β -defensins and mucins, as well as induction of cytokines and chemokines, in particular IL-6, IL-8, and GM-CSF (Pappu et al., 2012). Functional studies indicated that IL-17A and IL-17F play an important role in protective immunity against bacteria, fungi, and parasites (Iwakura et al., 2011; Kelly et al., 2005; Kim et al., 2012; Lockhart et al., 2006). In humans, defective expression of IL-17A and IL-17F was associated with the development of rheumatoid arthritis, multiple sclerosis, asthma, inflammatory bowel disease, as well as allograft rejection and tumor development (Iwakura et al., 2011; Pappu et al., 2012). Given that homodimers of IL-17A and IL-17F bind to the same receptor, albeit with different affinities, it has been suggested that these cytokines possess overlapping, yet distinct, biological activities (Iwakura et al., 2011). Differences in their functional properties also may be related to the different tissue distribution patterns of IL17A vs. IL-17F (Reynolds et al., 2010).

IL-17B is expressed in multiple organs, including pancreas, small intestine, stomach, spinal cord, and testis (Li et al., 2000; Shi et al., 2000). Unlike IL-17A and IL-17F, the IL-17B homodimer alone binds to IL-17RB (Iwakura et al., 2011; Pappu et al., 2010). IL-17B stimulated the release of IL-1 β and TNF- α in the THP-1 monocyte cell line and was chemotactic for neutrophils (Li et al., 2000; Pappu et al., 2010; Shi et al., 2000). Recombinant IL-17B inhibited endothelial cell-matrix adhesion and cellular migration

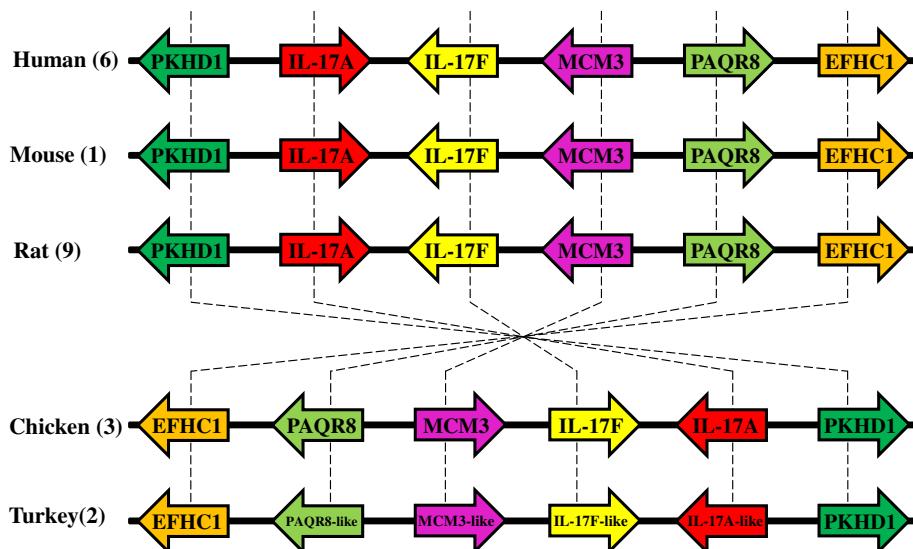


Fig. 1. Schematic illustration of the mammalian and avian genomes in the region of the IL-17A and IL-17F genes. Chromosome numbers are indicated in parentheses. PKHD1, polycystic kidney and hepatic disease 1; MCM3, minichromosome maintenance complex component 3; PAQR8, progestin and adiponQ receptor family VIII; EFHC1, EF-hand domain (C-terminal) containing 1.

(Sanders et al., 2010). High levels of IL-17B protein were detected in primitive and prehypertrophic chondrocytes after fracture, and in chondrocytes of normal bovine articular cartilage (Moseley et al., 2003; Kokubu et al., 2008). Increased expression of IL-17B was observed in a murine model of collagen-induced arthritis, and adoptive transfer of IL-17B-expressing CD4⁺ T cells exacerbated disease pathology and augmented TNF- α production (Yamaguchi et al., 2007). Treatment with IL-17B neutralizing antibody suppressed these symptoms.

IL-17C shares 27% amino acid sequence identity with IL-17A (Li et al., 2000). IL-17C binds to the IL-17RA/IL-17RE heterodimer receptor complex (Gaffen, 2009; Ramirez-Carrozzi et al., 2011). IL-17A mRNA levels were up-regulated in the lungs of mice infected with *Mycoplasma pneumoniae*, in epidermal keratinocytes following *Staphylococcus aureus* infection, in mononuclear cells from synovial fluid of rheumatoid arthritis patients, and in peripheral blood mononuclear cells (PBMC) from normal individuals treated with IL-15 (Holland et al., 2009; Hwang and Kim, 2005; Wu et al., 2007). IL-17C protein was detected in colonic epithelial cells, tracheal epithelial cells, and keratinocytes following treatment with heat-killed *Citrobacter rodentium* (Ramirez-Carrozzi et al., 2011; Song et al., 2011). Finally, IL-17C promoted inflammation in a mouse model of psoriasis and exerted protective functions in dextran sodium sulfate-induced murine colitis (Ramirez-Carrozzi et al., 2011).

IL-17D is a protein of 202 amino acids that exhibits greatest amino acid sequence identity with IL-17B (27%) (Starnes et al., 2002). Similar to IL-17B, IL-17D is expressed in a wide range of tissues and organs, including skeletal muscle, brain, adipose tissue, heart, lung, pancreas, and thymus. IL-17D stimulated the expression of IL-6, IL-8, and GM-CSF by human endothelial cells, as well as IL-6 and IL-8 by chicken embryonic fibroblast (Hong et al., 2008; Starnes et al., 2002). IL-17D gene expression was increased in osteoblast-like cells (MC3T3-E1) upon compressive force stimulation (Zhang et al., 2010). The receptor(s) for IL-17D is unknown.

The IL-17E protein displays 25–35% sequence identity with other IL-17 family members and binds the IL-17RA/IL-17RB receptor complex (Kim et al., 2002; Iwakura et al., 2011). IL-17E activated NF- κ B and induced the production of IL-8 by human 293 and TK-10 kidney cells (Lee et al., 2001). IL-17E promoted IL-9 expression by Th9 cells, a distinct subpopulation of CD4⁺ T cells that preferentially secretes IL-9 and IL-10 (Angkasekwainai et al., 2010; Reynolds et al., 2010). In addition, IL-17E mRNA was expressed in a variety of other cell types, including IgE-activated mast cells, alveolar macrophages, microglia, eosinophils, basophils, epithelial cells, and endothelial cells (Iwakura et al., 2011; Reynolds et al., 2010). The IL-17E gene transcript was detected in highly polarized Th2 cells, and IL-17E stimulated the expression of IL-4, IL-5, and IL-13, resulting in a Th2-mediated immune response marked by eosinophilia and elevated serum IgE levels (Iwakura et al., 2011; Kim et al., 2002). IL-17E induced Th2 cytokine-independent airway hyper-responsiveness (AHR), eosinophil lung infiltration, and mucus hypersecretion (Sharkhuu et al., 2006). AHR was suppressed in mice treated with IL-17E neutralizing antibody (Ballantyne et al., 2007). The number of IL-17E-producing cells was significantly higher in asthmatic bronchial mucosa compared with disease-free controls (Corrigan et al., 2011). However, IL-17E expression was decreased in epithelial and macrophage-like cells of inflammatory bowel diseases (IBD) patients (Caruso et al., 2009). IL-17E treatment attenuated peptidoglycan-, 2,4,6-trinitrobenzenesulphonic acid-, or oxazolone-induced colitis in mice (Caruso et al., 2009). Administration of IL-17E recombinant protein decreased tumor outgrowth in mice, and promoted eosinophil recruitment into tumor sites (Benatar et al., 2008, 2010). Finally, IL-17E was constitutively produced by CD4⁺ and CD8⁺ T cells in the gut of mice resistant to *Trichuris muris*

infection (Owyang et al., 2006). Taken together, these results suggest that IL-17E plays a role in the pathogenesis of allergic inflammatory diseases, prevention of helminth infections, and antitumor activities.

4.2. Piscine IL-17s

Using the zebrafish genome database, cDNAs encoding five IL-17 cytokine-related genes were initially identified in 2006, displaying 19–62% amino acid sequence identity with their corresponding human proteins (Gunimaladevi et al., 2006). The fish IL-17 family now includes seven members, IL-17A/F1, IL-17A/F2, IL-17A/F3, IL-17C1, IL-17C2, IL-17D, and IL-17N. IL-17N is unique to fish (Korenaga et al., 2010; Kono et al., 2011; Secombes et al., 2011). Fish homologues of mammalian IL-17B and IL-17E have not been identified. Three IL-17Rs (IL-17RA, IL-17RB, and IL-17RD) have also been characterized in fish. The three zebrafish IL-17A/F1, IL-17A/F2, and IL-17A/F3 genes consist of three exons and two introns. However, the genomic structure of the Japanese pufferfish (*Takifugu rubripes*, or fugu) IL-17A/F3 gene is composed of four exons and three introns. In zebrafish, IL-17A/F1 mRNA was detected only in the intestine, IL-17A/F2 in the kidney, gill, and intestine, and IL-17A/F3 in the gill and intestine (Gunimaladevi et al., 2006). In fugu, the IL-17A/F1 transcript was observed in the brain and gill. By comparison, fugu IL-17A/F2 mRNA was highly expressed in the skin, whereas fugu IL-17A/F3 was detected in all tissues examined (Korenaga et al., 2010). The differential expression pattern of the IL-17A/F1, IL-17A/F2, and IL-17A/F3 genes among these fish species may reflect dissimilar biological functions of their encoded gene products.

IL-17C1 and IL-17C2 have been described in fugu and rainbow trout. Both consist of three exons and two introns, similar to human IL-17C (Gunimaladevi et al., 2006; Korenaga et al., 2010; Wang et al., 2010). Expression of trout IL-17C1 and IL-17C2 transcripts was detectable in a variety of normal tissues, with relatively high expression in the gill and skin (IL-17C1), and in the spleen, head-kidney, and brain (IL-17C2). Fugu IL-17C1 was highly expressed in the head-kidney, while IL-17C2 was preferentially present in the brain and gill. IL-17C2 expression was elevated in the spleen of trout infected with *Yersinia ruckeri*, and upon stimulation with a monocyte/macrophage cell line with LPS, poly(I:C), calcium ionophore, IL-1 β , or IFN- γ .

The IL-17D gene of zebrafish, fugu, and Atlantic salmon consists of two exons and one intron (Gunimaladevi et al., 2006; Kumari et al., 2009; Korenaga et al., 2010). The salmon IL-17D gene transcript was widely expressed in normal tissues, with highest expression in the testes, ovary, and skin. The expression of IL-17D was increased in the head-kidney, but not the spleen, of salmon following *Aeromonas salmonicida* infection. Salmon IL-17D expression was elevated in a time-dependent manner in the spleen and head-kidney after injection of LPS and β -glucan. Fugu IL-17N mRNA was highly expressed in the head-kidney, heart, spleen, and gill (Korenaga et al., 2010), whereas that of Japanese rice fish (*Oryzias latipes*) was observed only in the kidney and brain (Kono et al., 2011).

4.3. Avian IL-17s

Despite the fact that the chicken genome was sequenced in 2004 (International Chicken Genome Sequencing Consortium, 2004.), the identification of avian cytokine genes, in general, has been difficult due to low sequence homology with their mammal counterparts (Staeheli et al., 2001). To date, only three IL-17s have been identified in avians, IL-17A, IL-17D, and IL-17F (Fig. 2). Genomic analysis identified a possible orthologue of mammalian IL-17B on chicken chromosome 13 (Kaiser et al., 2005). However, no evi-

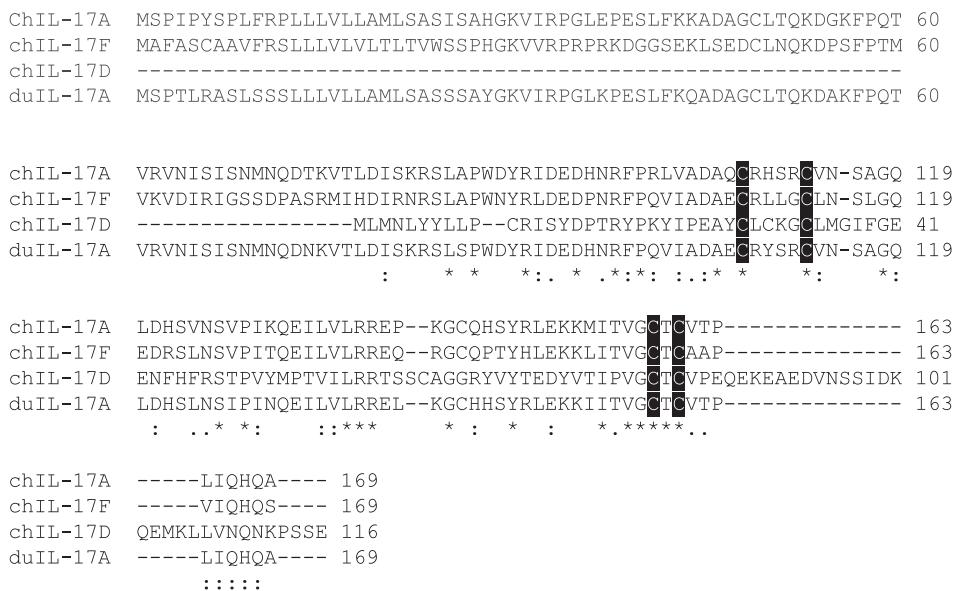


Fig. 2. Multiple alignments of the avian IL-17A, IL-17D, and IL-17F amino acid sequences deduced from nucleotide sequences. Alignments were made using ClustalW2 (www.ebi.ac.uk/Tools/msa/clustalw2/). Asterisks (*) indicate identical residues. Double dots (:) indicate conserved residues. Single dots (.) indicate semi-conserved residues. Dashes (-) indicate gaps to maximize alignments. The four cysteine residues conserved are indicated by black boxes. The GenBank accession numbers used in the comparison are AJ93595 (chicken IL-17A), ABU51881 (chicken IL-17D), JQ776598 (chicken IL-17F), and EU366165 (duck IL-17A).

dence for chicken IL-17C or IL-17E genes or gene products has been published. In addition, little information is available concerning avian IL-17Rs.

The chicken IL-17A gene was first cloned from an EST cDNA library prepared from intestinal IEIs of *E. acervulina*-infected chickens (Min and Lillehoj, 2002). The chicken IL-17A gene transcript was detected in a reticuloendotheliosis virus-transformed chicken lymphoblast cell line (CU205) and conconavalin A (ConA)-stimulated spleen lymphocytes, but not in a variety of normal bird tissues. Chicken IL-17A protein consists of 169 amino acids, including six conserved cysteine residues that form intrachain disulfide bonds that are preserved among all IL-17As and HVS13. Chicken IL-17A shares 37–46% amino acid sequence identity with mammalian IL-17s and HVS13.

The duck IL-17A gene was cloned from ConA-activated spleen lymphocytes (Yoo et al., 2009). This gene was predicted to encode a protein of 169 amino acids that shares 84% sequence identity with chicken IL-17A, including the six conserved cysteine residues, but 36–47% sequence identity with the corresponding mammalian proteins. Similar to chicken IL-17A, duck IL-17A mRNA was detected only in ConA-activated spleen lymphocytes and not in normal tissues. Mouse monoclonal antibodies against chicken IL-17A recognized the 20–21 kDa duck IL-17A monomer on Western blots of ConA-activated spleen cells, but not unstimulated lymphocytes.

The chicken IL-17D gene was identified in a testis cDNA library prepared from Korean native chickens (Hong et al., 2008). It was predicted to encode a 116 amino acid protein, including six conserved cysteine residues. These cysteines include the four residues that are conserved among all mammalian, piscine, and avian IL-17s, plus two residues that are found in IL-17Ds, but not IL-17As or IL-17Fs. Further, the sequence of chicken IL-17D is more homologous to mammalian IL-17Ds (53–76%) than is chicken IL-17A with mammalian IL-17As (37–46%). The chicken IL-17D transcript, like that of the human mRNA, was expressed in a wide range of tissues.

The chicken IL-17F gene was cloned from ConA-activated chicken spleen lymphocytes (Kim et al., 2012). It's predicted 169 amino acid polypeptide shares 53% sequence identity with chicken IL-17A, 18% with chicken IL-17D, and 38–43% with mammalian IL-17Fs. The chicken IL-17F transcript was detected at low levels in

most normal tissues. Treatment of primary chicken embryonic fibroblasts with recombinant chicken IL-17A and IL-17F proteins increased the production of IL-1β, IL-6, and IL-8. However, unlike human IL-17F, which stimulated TGF-β1 expression by endothelial cells (Starnes et al., 2002), chicken IL-17F did not stimulate TGF-β1 (or TGF-β4 in chickens) expression (Kim et al., 2012).

5. Role of IL-17 cytokines in protozoan and helminthic infections

5.1. Protozoan infections other than *Eimeria*

In protozoan and helminthic infections, IL-17 family cytokines exert either protective or pathogenic effects, depending on the pathogen, host, and conditions of infection (Gaddi and Yap, 2007; Guiton et al., 2010; Pappu et al., 2010; Reynolds et al., 2010; Larkin et al., 2012). In the case of human leishmaniasis, IL-17A expression was generally increased compared with uninfected subjects, suggesting a defensive role of the cytokine (Soong et al., 2012). Increased numbers of IL-17A-producing CD4⁺ T cells were noted in the peripheral blood of humans infected with *Plasmodium vivax* malaria (Bueno et al., 2012). IL-17A-producing CD4⁺CD25⁺Foxp3^{int} cells were elevated in *in vitro* co-cultures of PBMCs with malaria-infected red blood cells (Scholzen et al., 2009). By contrast, IL-17A-producing CD4⁺ T cell numbers were reduced in humans co-infected with malaria (*Plasmodium falciparum*) and filarial (*Wuchereria bancrofti*) parasites, compared with those infected with malaria alone (Metenou et al., 2011). Decreased IL-17A mRNA levels were seen in regional lymph nodes of *Plasmodium chabaudi*-infected mice in the context of experimental autoimmune encephalomyelitis (EAE), compared with transcript levels in EAE alone (Farias et al., 2011).

IL-17RA knockout mice challenged with *T. gondii* displayed increased parasite burden in the spleen, liver, gut, and brain, but reduced mucosal damage which was attributed to diminished neutrophil migration to infected sites (Kelly et al., 2005). Mice expressing IL-17RA and orally infected with *T. gondii* showed increased IL-17A and IL-17F gene transcript levels in the inflamed ileum compared with uninfected mice (Guiton et al., 2010).

Prolonged survival following *T. gondii* infection was observed both in IL-17RA knockout mice and wild type mice treated with IL-17A neutralizing antibody compared with the corresponding controls. IL-17A mRNA levels were decreased in CD4⁺ T cells of mesenteric lymph nodes and spleen of *T. gondii*-infected mice deficient in the expression of the IL-1 receptor agonist, a model of rheumatoid arthritis (Washino et al., 2012).

Trypanosoma congolense-susceptible BALB/c mice had enhanced levels of IL-17A-producing CD4⁺ T cells in the spleen and liver compared with the relatively trypanosomiasis-resistant C57BL/6 mice (Mou et al., 2010). Increased IL-17A-producing CD4⁺ T cell numbers were observed in the spleens of *Trypanosoma cruzi*-infected C57BL/6 mice compared with uninfected controls (Santamaria and Corral, 2013). Treatment of *T. cruzi*-infected mice with an IL-17A neutralizing antibody increased parasitemia, whereas injection of IL-17A recombinant protein had the opposite effect. IL-17A/F2 gene expression was up-regulated in the head-kidney of *Trypanosoma carassii*-infected carp, but not following *Trypanosoma borrelii* infection (Ribeiro et al., 2010).

5.2. Helminthic infections

Increased IL-17A protein levels were detected in the plasma of BALB/c and C57BL/6 mice infected with *Schistosoma mansoni* compared with uninfected controls (Tallima et al., 2009). The percentages of IL-17A-producing cells were higher in the peripheral blood, spleen, and granulomas of high pathology CBA/J mice compared with low pathology C57BL/6 mice following *S. mansoni* infection (Mbow et al., 2013). Administration of IL-17A neutralizing antibody decreased hepatic immunopathology and reduced worm burden following *S. japonicum* infection of C57BL/6 mice compared with untreated animals (Wen et al., 2011). In humans, *S. haematobium*-infected children with clinical signs of infection showed higher a percentage of Th17 cells in peripheral blood compared with infected subjects without pathology (Mbow et al., 2013). These latter results support the proposal by Larkin et al. (2012) that IL-17 cytokine responses in human schistosomiasis show marked differences in genetically disparate hosts.

Elevated numbers of IL-17A-producing cells were found in nasal biopsies of patients afflicted with mucosal leishmaniasis compared with disease-free controls (Boaventura et al., 2010). In contrast, the percentage of CD3⁺CD4⁺IL-17A⁺ cells was decreased in PBMCs from patients with mucosal leishmaniasis cointfected with HIV following *in vitro* stimulation with *Leishmania brasiliensis* antigen compared with unstimulated controls (Castellano et al., 2011). IL-17A gene transcripts were increased in skin biopsies of post-kala azar dermal leishmaniasis patients infected with *Leishmania donovani* compared with uninfected controls (Katara et al., 2012). In a mouse model of cutaneous leishmaniasis, infection by *Leishmania major* increased IL-17A production by CD4⁺ T cells and neutrophils in susceptible BALB/c mice compared with the more resistant C57BL/6 strain (Kostka et al., 2009). IL-17A knockout BALB/c mice exhibited decreased lesion size and reduced parasite burden compared with wild type littermates following experimental *L. major* infection.

IL-17E knockout mice were unable to efficiently eradicate infections by *Nippostrongylus brasiliensis*, a natural rodent nematode closely related to human hookworms, or *T. muris*, a mouse nematode related to human roundworms, compared with IL-17E-expressing animals (Fallon et al., 2006; Owyang et al., 2006; Saenz et al., 2010; Zhao et al., 2010). Similarly, compared with wild type littermates, IL-17RB knockout mice, which lack a functional IL-17E receptor, exhibited a reduced capacity to eradicate infection by *N. brasiliensis* (Neill et al., 2010). IL-17E mRNA expression was up-regulated in the intestine of mice infected with *N. brasiliensis*, *T. muris*, or *Heligmosomoides polygyrus* compared with uninfected controls (Zhao et al., 2010). *In vivo* admin-

istration of IL-17E recombinant protein led to more rapid parasite expulsion in murine infections with *N. brasiliensis* or *T. muris* compared with untreated controls (Fallon et al., 2006; Owyang et al., 2006; Price et al., 2010).

IL-17A production by mononuclear cells from the intestinal lamina propria and mesenteric lymph nodes was reduced in mice colonized with *H. polygyrus*, a common nematode found in the duodenum and small intestine of rodents, compared with uninfected animals (Elliott et al., 2008). The expression of IL-17A mRNA was up-regulated in Peyer's patches and intestinal tissues of *Echinostoma caproni*-infected rats, a low compatibility host, but not in mice, a high compatibility host, compared with uninfected controls (Sotillo et al., 2011). In mice with experimental EAE, infection with *Fasciola hepatica*, the common liver fluke, attenuated clinical signs and reduced IL-17A production by antigen-stimulated spleen cells compared with uninfected controls (Walsh et al., 2009).

6. Role of IL-17 cytokines in avian coccidiosis

6.1. Chicken IL-17A

Following primary infection by *E. acervulina* or *E. maxima*, IL-17A mRNA levels were generally increased in intestinal IELs when measured by a quantitative RT-PCR compared with uninfected controls (Hong et al., 2006a,b). The maximum increases in IL-17A expression were 2,020-fold at *E. acervulina* post-infection day 5 and 1,650-fold *E. maxima* post-infection day 4. In the case of *E. tenella*, IL-17A expression by gut lymphocytes following primary infection was generally down-regulated, except at day 10 post-infection when a modest 3-fold increase was seen. Similarly, Kim et al. (2012) reported that IL-17A expression was down-regulated in the gut following primary infection with *E. tenella*. Chickens co-infected with *E. maxima* and *Clostridium perfringens*, the etiologic agent of avian necrotic enteritis, had decreased intestinal IL-17A transcript levels compared with animals infected with *C. perfringens* alone (Park et al., 2008). These results suggest that the manner of IL-17A expression in the gut is dependent on the species of infecting *Eimeria* as well as the time post-infection.

Given that some studies have demonstrated that *Eimeria* infection reduces IL-17A expression in the gut, a variety of immunomodulation strategies that increase IL-17A expression have been attempted in an effort to promote protective immunity against avian coccidiosis. Feed supplementation with phytase (myo-inositol hexakisphosphate phosphohydrolase), vaccination with CoccivacB (Intervet/Schering-Plough Animal Health, Millsboro, DE), or litter seeding with *E. acervulina* and *E. tenella* significantly increased IL-17A transcript levels in the intestinal duodenum compared with the respective controls (Shaw et al., 2011). Chickens immunized against *Eimeria* infection using a profilin subunit vaccine had increased IL-17A transcripts in the duodenum following infection with *E. acervulina* compared with unvaccinated controls (Lee et al., 2010, 2011). However, profilin vaccination in combination with a phytonutrient-supplemented diet decreased IL-17A transcripts in the cecal tonsils of *E. tenella*-infected chickens compared with vaccinated birds given a non-supplemented diet (Lee et al., 2010, 2011). Vaccination of chickens with another recombinant protein, *E. tenella* microneme protein 2 (EtMIC2), also enhanced IL-17A expression in gut lymphocytes compared with unimmunized controls, and vaccination with EtMIC2 plus *E. tenella* heat shock protein 70 (EtHSP70) further increased IL-17A levels compared with EtMIC2 or EtHSP70 alone (Zhang et al., 2012).

On the basis of the aforementioned studies, chicken recombinant IL-17A has been tested as a vaccine adjuvant against experimental *Eimeria* infection. Treatment of chickens with IL-17A alone, either as a purified recombinant protein or a DNA vaccine

encoded by an expression plasmid, did not influence the course of experimental *Eimeria* infection compared with untreated controls (Lillehoj, unpublished observations). However, immunization of chickens with a chimeric DNA vaccine encoding the *E. tenella* surface antigen, MZP5-7, and the IL-17A gene downstream of MZP5-7 reduced fecal oocyst shedding and decreased the severity of intestinal lesions following experimental *E. tenella* infection compared with immunization with MZP5-7 alone (Geriletu et al., 2011). Similarly, simultaneous immunization of chicken embryos with a purified recombinant profilin protein plus an expression plasmid encoding the IL-17A gene increased serum antibody responses against profilin and improved protective immunity against experimental *E. acervulina* coccidiosis in the post-hatch animals compared with animals given profilin alone, or compared with animals given profilin plus cDNAs for other recombinant cytokines (IL-2, IL-6, IL-8, or IFN- γ) (Ding et al., 2004). Interestingly, however, embryo co-vaccination with cDNAs for profilin and IL-17A did not increase protective immunity against subsequent challenge infection by *E. tenella* compared with profilin alone (Lillehoj et al., 2005b). Further, embryo co-vaccination with EtMIC2 recombinant protein plus the IL-17A gene also did not influence the course of experimental *E. tenella* infection compared with EtMIC2 alone (Lillehoj et al., 2005a). Future studies will be needed to determine the optimal conditions that reproducibly show IL-17A as a vaccine adjuvant in avian coccidiosis.

6.2. Chicken IL-17D, IL-17F, and non-avian models of coccidiosis

Chicken IL-17D mRNA levels were increased in total intestinal tissues of chickens infected with *E. maxima* compared with uninfected controls (Hong et al., 2008). *E. maxima*-infected chickens also expressed increased IL-17D mRNA levels in gut total IELs as well as CD4 $^+$, CD8 $^+$, and $\gamma\delta$ TCR $^+$ IELs, but decreased levels in $\alpha\beta$ TCR $^+$ IELs, compared with uninfected chickens. Similarly, chicken IL-17F transcripts were elevated in intestinal tissues from *E. maxima*- or *E. tenella*-infected animals compared with uninfected controls (Kim et al., 2012). Treatment of an *E. falciformis*-infected mouse intestinal epithelial cell line with IL-17A purified recombinant protein reduced *in vitro* parasite development compared with untreated cells (Stange et al., 2012). *E. falciformis*-infected IFN- γ knockout and IFN- γ receptor knockout mice had fewer post-infection intestinal parasites compared with wild type littermates, although weight loss and intestinal pathology were increased. Finally, increased *in vitro* parasite-stimulated IL-17A production by CD4 $^+$ T cells from the mesenteric lymph nodes and intestine were observed in infected animals compared with uninfected controls (Stange et al., 2012).

7. Conclusion

The complex interplay among immune effector cells and their secreted cytokines and chemokines, the intestinal epithelia, and the gut microbiota ultimately determines host susceptibility or resistance to infectious pathogens. One of the current challenges of avian coccidiosis research is to identify the cellular and molecular basis for species-specific immunity and a potential cross-protective immune mechanism that could confer protection against multiple species of *Eimeria*. In addition, the role of soluble factors that mediate local inflammatory responses requires further characterization, particularly in view of the negative consequences of uncontrolled inflammation on gut health and poultry productivity. Although traditionally thought of as a component of adaptive immunity, Th17-related cytokines are now recognized as part of the rapid response that develops during the initial phases of immune system activation. Once secreted, these cytokines, and

others, regulate the interactions between mucosal epithelia and their associated lymphocytes to eradicate invading pathogens, and to restore immune homeostasis. In the case of avian coccidiosis, the immunoregulatory roles of the newly described proinflammatory IL-17 cytokine family in the host response to parasite infection deserves continued study. With the availability of the complete sequence of the chicken genome, combined with new molecular, genetic, immunologic, and nutritional technologies to assess and manipulate the host immune response to avian coccidiosis, more effective disease control strategies will undoubtedly become a reality in the future.

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